Bacteriotherapy in children with recurrent upper respiratory tract infections

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Abstract. – OBJECTIVE: Children with recurrent upper-airway infections (UI) represent a social issue for their economic burden and negative impact on families. Bacteriotherapy is a new therapeutic strategy that could potentially prevent infections. The current study tested the hypothesis that recurrent UI may be prevented by bacteriotherapy.

PATIENTS AND METHODS: This open study was conducted in an outpatient clinic, enrolling 80 children (40 males, mean age 5.26±2.52 years) suffering from recurrent UI. Children were treated with a nasal spray containing *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a, 2 puffs per nostril twice a day for a week; this course was repeated for 3 months. The evaluated parameters were: number of UI and number of school and work absences; these outcomes were compared with those recorded in the past year.

RESULTS: The mean number of UI significantly diminished: from 5.98 (2.30) in the past year to 2.75 (2.43) after treatment (*p*<0.0001). The number of school and work absences significantly diminished (from 4.50±2.81 to 2.80±3.42 and from 2.33±2.36 to 1.48±2.16 respectively; *p*<0.0001 for both).

CONCLUSIONS: This preliminary experiment suggests that bacteriotherapy using *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a nasal spray could prevent recurrent UI in children.

Key Words
Recurrent upper-airway infections, Bacteriotherapy, Prevention, Streptococcus salivarius 24SMB, Streptococcus oralis 89a, Nasal spray, Children.

List of Abbreviations

UI: upper-airway infections; IQR: interquartile range.

Introduction

Children with recurrent upper-airway infections (UI) represent a substantial burden for healthcare services and a considerable inconvenience for the family[1-3].

Many factors may cause UI recurrence, mainly early age (because of the relative immaturity of the immune system), early attendance at nursery school, environmental pollution, passive smoking, low socioeconomic level, and allergic disorders [2]. Notably, viral infections exercise a crucial role as the most common cause of respiratory infection in childhood[3]. Bacterial secondary infections may frequently complicate viral infection.

In common practice, UI is usually diagnosed on clinical grounds, such as patient history and the presence of typical signs and symptoms. The common guidelines define the appropriate use of anti-inflammatory drugs and antibiotics, but pediatricians and otolaryngologists often really prescribe on an empiric basis in clinical practice[3,4]. Anti-inflammatory agents may have adverse effects in children that complicate the course of disease and treatment. Antibiotics produce resistant bacteria, which in addition to broader public health concerns, can affect the course of treatment and especially of recurrence. Effective prevention of recurrent UI could significantly reduce complications and medical costs and improve the social and family burden.

Several prevention strategies have been trialed; however, these attempts were frequently ineffective and seldom dangerous[5]. Prevention of recurrent UI poses an intriguing challenge for the researcher and the clinician.

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Consideration of the microbiome offers one way to explore prevention by way of manipulating resident microbes[5,6]. The "normal" nasopharyngeal microbiome inhibits pathogens. As a consequence, it has been hypothesized that administration of "good" bacteria could prevent recurrent infections by limiting pathogenic growth. It has been previously reported that a-hemolytic strain (*Streptococcus salivarius* 24SMB), obtained from healthy children and administered as a nasal spray, reduced the recurrence of acute otitis media in otitis-prone children[7]. A further study showed that *Streptococcus salivarius* 24SMB, along with *Streptococcus oralis* 89a, was effective in preventing recurrent otitis in a real-life setting [8]. The current experiment aimed to evaluate the possible preventive effect of such bacteriotherapy in a cohort of children suffering from recurrent UI.

Patients and methods

Patients

The present experiment included 80 children (40 males, mean age 5.26 ± 2.52years) with a history of recurrent UI in the past year. Inclusion criteria were: i) age ranging between 3 and 14 years, ii) comparable numbers of both genders, iii) documented history of recurrent UI in the past year, iv) written informed consent by parents. Exclusion criteria were: i) severe allergic symptoms (such as might interfere with assessment of treatments), ii) congenital or acquired immunodeficiency, iii) craniofacial abnormalities, iv) sleep apnea, v) Down syndrome, vi) chronic disease (including metabolic disorders, cystic fibrosis, cancer, etc.), vii) clinically relevant passive smoking, and viii) previous (last 3 months) or current administration of drugs able to interfere with the study (e.g. immunomodulants, homeopathic therapy, or systemic corticosteroids for at least 2 consecutive weeks). The study was specifically approved by the Ethical Committee of our University Hospital.

Study Design

The current experiment was designed as an open study. Children with UI were visited by the otolaryngologist to ensure proper case management. Children were treated with a commercially available, class IIa medical device: nasal spray containing *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a (Rinogermina, DMG, Rome, Italy). It was administered as 2 puffs per nostril twice a day for 7 days. The suspension consisted of a minimum of 10^9 colony-forming units per dose. This course was administered for 3 consecutive months. As bacteriotherapy has been shown to have a preventive effect, the first course usually started in the early autumn, based on symptom history and seasonal expectations.

The number of UI, and the number of missed days of school or work (for parents) were compared, using data from the prior year and status at follow up. The presence of siblings and passive smoking were considered as additional variables in the evaluation.

Safety

Safety and tolerability were evaluated on the basis of the number and type of adverse events recorded.

Study Procedures

UI was diagnosed on the basis of the symptoms reported by the parents, as previously defined in the literature[9]. UI diagnosis was made when at least 2 symptoms (detailed below) or fever (axillary temperature ≥38°C) in addition to one other symptom, were present for at least 48 hours. The considered symptoms were: mucopurulent rhinorrhoea, stuffy or dripping nose or both, sore throat, cough (dry or productive), otalgia (earache), fever, and mucopurulent secretion. Recurrent UI diagnosis was based on history and included patient's and/or parents' recall of symptoms.

The children were examined at study entry, and at the follow-up re-evaluation (in the summer). All assessed parameters were regularly recorded on a daily diary card.

Statistical Analysis

Demographic and clinical characteristics are described using means with SDs for normally-distributed continuous data (i.e. age) or medians with lower and upper quartiles and interquartile range (IQR), for not normally-distributed data. Any statistically significant difference in the median values of each continuous variable (UI number, number of school days or work days missed per month between pre- and post-treatment with Rinogermina), or between patients with more or less frequent UI episodes was evaluated with the Wilcoxon signed rank test or the Mann U Whitney test, respectively. Correlations were evaluated with Spearman rank-order correlation coefficient. Statistical significance was set at $p < 0.05$, and the analyses were performed using GraphPad Prism software (GraphPad Software Inc., La Jolla, CA, USA).

Results

Forty males and forty females were enrolled. Patient age at the beginning of treatment was 5.26 (2.52) years; most children were preschoolers (57, 71.25%). Mean treatment period was 88.59 (32.54) days, with a mean follow-up duration of 132.00 (40.90) days. All treatments were well tolerated, and no clinically relevant adverse effect was observed.

Bacteriotherapy halved the mean number of UI episodes from 6 (IQR 4.25-7) in the past year to 2 (IQR 1-4) after treatment ($p<0.0001$, Figure 1). Bacteriotherapy also reduced by about 35% both the number of school days and the number of work days missed per month, from 5.0 (IQR 2.0-6.0) to 2 (IQR 0-5) and from 2 (IQR 0-4.75) to 0 (IQR 0-2), respectively ($p<0.0001$, Figures 2 and 3).

The number of UI episodes strongly correlated with the number of school days missed per month (r=0.678, $p<0.001$, Figure 4A). A moderate correlation was detected between the number of UI episodes and the number of work days missed per month (r=0.514, $p<0.001$, Figure 4B). As expected, the number of school days missed per month strongly correlated with the number of workdays missed (r=0.605, $p<0.0001$, Figure 5).

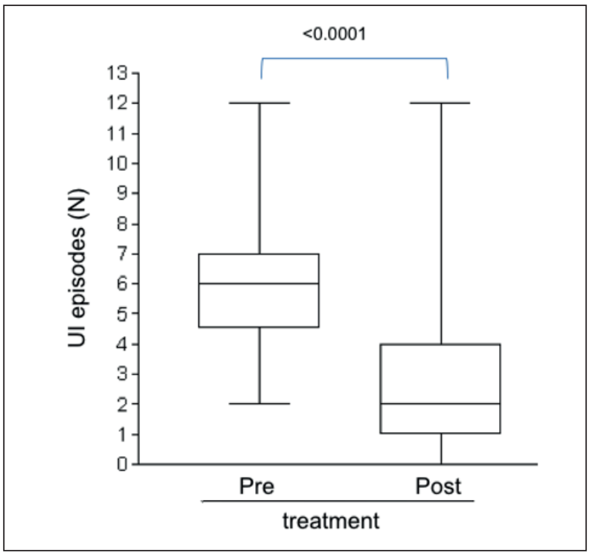

Figure 1. Number of UI episodes in the past year before (Pre) and after treatment with Rinogermina (Post). The horizontal lines represent (from the top) the maximum, the upper quartile, the median, the lower quartile and the minimum.

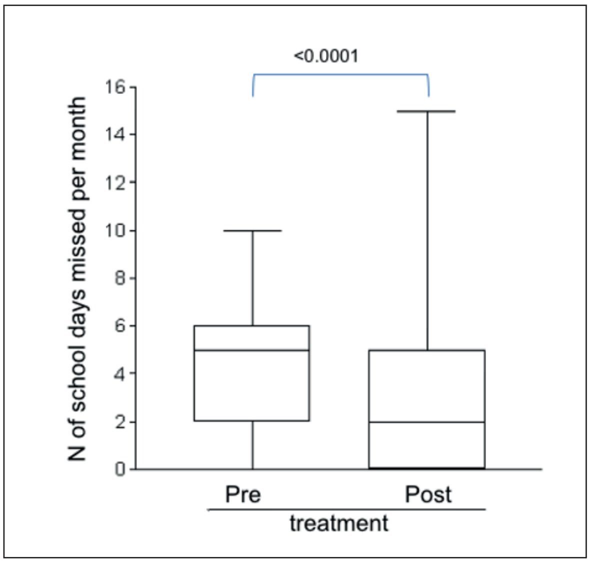

Figure 2. Number of school days missed per month before and after treatment with Rinogermina. The horizontal lines represent (from the top) the maximum, the upper quartile, the median, the lower quartile and the minimum.

No correlations were found between changes in the number of UI episodes after bacteriotherapy and patient age at the beginning of treatment (r=0.076, $p=0.50$; not shown).

Sibling presence and allergy did not affect any result. Passive smoking was significantly associated only with school absence ($p=0.02$; not shown).

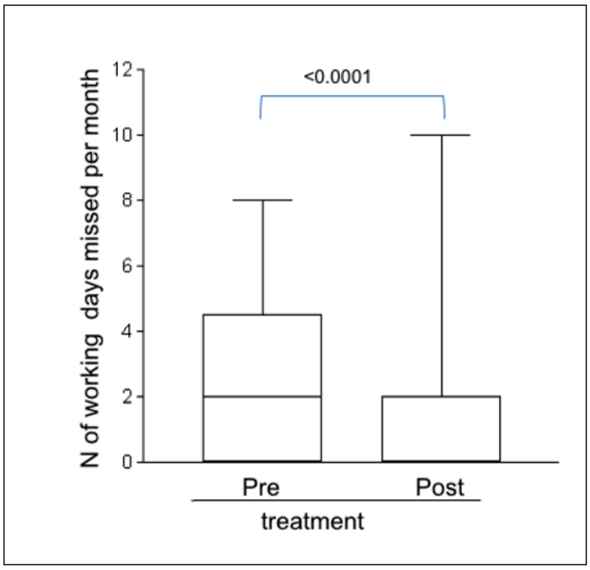

Figure 3. Number of workdays missed per month before and after treatment with Rinogermina. The horizontal lines represent (from the top) the maximum, the upper quartile, the median, the lower quartile and the minimum.

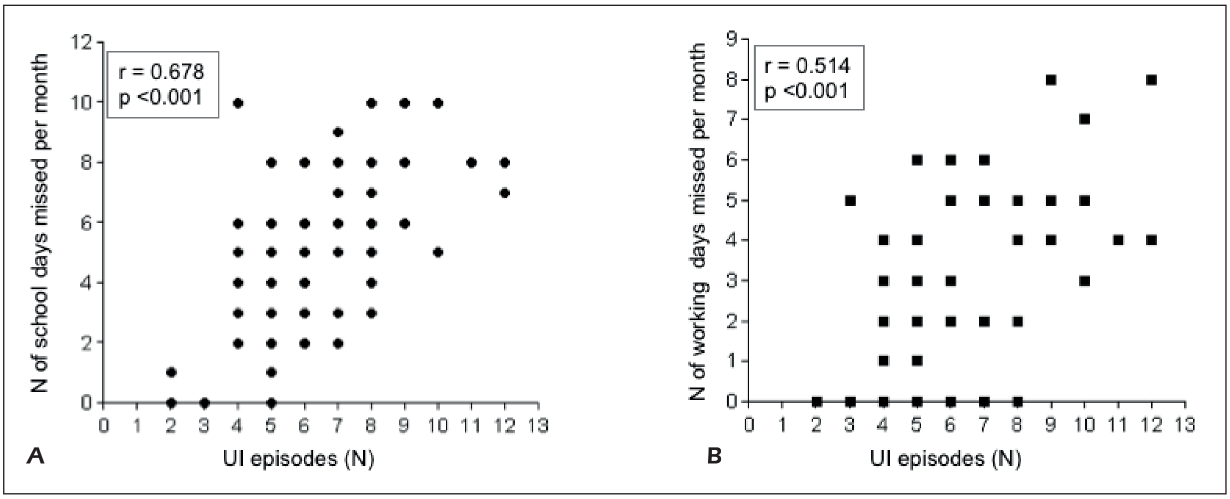

Figure 4. Correlation between the number of URI episodes and the number of school days missed per month (panel **A**) or the number of workdays missed per month (panel **B**).

Discussion

Recurrent UI represents a demanding challenge for otolaryngologists and paediatricians. UI therapy guidelines advise limiting antibiotic prescription to more severe infections. This recommendation may be disregarded in clinical practice, where antibiotic therapy is commonly prescribed along with anti-inflammatory/antipyretic medications.

A similar disjunction exists in research. As one example, a recent placebo-controlled study investigated a 12-month treatment with azithromycin (5 mg/Kg/d) 3 d/week as preventive treatment for children with recurrent rhinosinusitis [10,11]. This schedule reduced the incidence of rhinosinusitis, amount of medication use, and symptom severity. On the other hand, long-lasting effects of azithromycin could induce resistance to macrolides, which is an emerging problem in many countries [12]. In our mind, there is room to explore alternative ways of preventing infections. Bacteriotherapy using so-called "good" bacteria could be a promising method [13]. The rationale is that some non-pathogenic physiological strains have been observed to protect from pathogen ("bad" bacteria) infections. The current experiment reports that *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a nasal spray could reliably prevent UI; of note, no adverse effects were reported; the compound was safe and well tolerated by all treated children. Bacteriotherapy significantly and consistently diminished UI as well as school and work absences. However, this study has some limitations: i) it was an open study; ii) it had no control-placebo group; iii) it was based only on clinical outcomes without cultural investigations; and iv) comparative data concerning the past year were retrospectively collected by parental queries. Further studies could be designed to overcome these limitations.

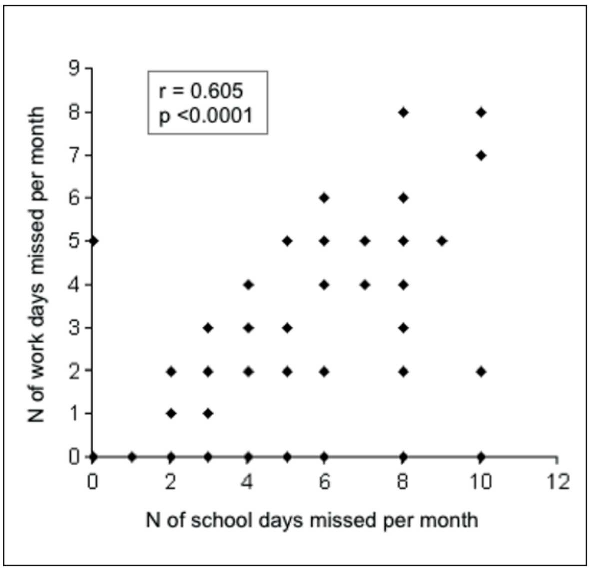

Figure 5. Correlation between the number of school days missed per month and the number of work days missed per month.

Conclusions

This preliminary study suggests that bacteriotherapy using *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a nasal spray could prevent recurrent upper-airway infections in children. However, the limits of the present study require further studies to correct for those limitations.

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Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Mansbach AL, Brihaye P, Casimir G, Dhooghe I, Gordts F, Halewyck S, Hanssens L, Lemkens N, Leupe P, Mulier S, Van Crombrugge L, Van Der Veken P, Van Hoecke H. Clinical aspects of chronic ENT inflammation in children. B-ENT 2012; 8 Suppl 19: 83-101.
2) Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, Batra PS, Bernal-Sprekelsen M, Bhattacharyya N, Chandra RK, Chiu A, Citardi MJ, Cohen NA, DelGaudio J, Desrosiers M, Dhong HJ, Douglas R, Ferguson B, Fokkens WJ, Georgalas C, Goldberg A, Gosepath J, Hamilos DL, Han JK, Harvey R, Hellings P, Hopkins C, Jankowski R, Javer AR, Kern R, Kountakis S, Kowalski ML, Lane A, Lanza DC, Lebowitz R, Lee HM, Lin SY, Lund V, Luong A, Mann W, Marple BF, McMains KC, Metson R, Naclerio R, Nayak JV, Otori N, Palmer JN, Parikh SR, Passali D, Peters A, Piccirillo J, Poetker DM, Psaltis AJ, Ramadan HH, Ramakrishnan VR, Riechelmann H, Roh HJ, Rudmik L, Sacks R, Schlosser RJ, Senior BA, Sindwani R, Stankiewicz JA, Stewart M, Tan BK, Toskala E, Voegels R, Wang de Y, Weitzel EK, Wise S, Woodworth BA, Wormald PJ, Wright ED, Zhou B, Kennedy DW. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. Int Forum Allergy Rhinol 2016; 6 Suppl 1: S22-209.
3) Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang de Y, Wormald PJ. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012; 50: 1-12.
4) Gisselsson-Solen M. Acute otitis media in children-current treatment and prevention. Curr Infect Dis Rep 2015; 17: 476.
5) Marchisio P, Nazzari E, Torretta S, Esposito S, Principi N. Medical prevention of recurrent acute otitis media: an updated overview. Expert Rev Anti Infect Ther 2014; 12: 611-620.
6) Pintucci JP, Corno S, Garotta M. Biofilms and infections of the upper respiratory tract. Eur Rev Med Pharmacol Sci 2010; 14: 683-690.
7) Marchisio P, Santagati M, Scillato M, Baggi E, Fattizzo M, Rosazza C, Stefani S, Esposito S, Principi N. Streptococcus salivarius 24SMB administered by nasal spray for the prevention of acute otitis media in otitis-prone children. Eur J Clin Microbiol Infect Dis 2015; 34: 2377-2383.
8) La Mantia I, Varricchio A, Ciprandi G. Bacteriotherapy with streptococcus salivarius 24SMB and streptococcus oralis 89a nasal spray for preventing recurrent acute otitis media in children: a real-life clinical experience. Int J Gen Med 2017; 10: 171-175.
9) Ciprandi G, Tosca MA, Fasce L. Allergic children have more numerous and severe respiratory infections than non-allergic children. Pediatr Allergy Immunol 2006; 17: 389-391.
10) Bakshi SS. Revisiting recurrent acute rhinosinusitis prevention by azithromycin in children. J Allergy Clin Immunol Pract 2017; 5: 1802.
11) Veskitkul J, Wongkaewpothong P, Thaweethamchareon T, Ungkanont K, Visitsunthorn N, Pacharn P, Vichyanond P, Jirapongsananuruk O. Recurrent acute rhinosinusitis prevention by azithromycin in children with nonallergic rhinitis. J Allergy Clin Immunol Pract 2017; 5: 1632-1638.
12) Stefani S, Mezzatesta M, Oliveri S, Nicolosi VM, Russo G. In vitro study of dactimicin (ST 900) against methicillin-susceptible and -resistant staphylococci. Chemioterapia 1987; 6: 264-268.
13) Campanella V, Syed J, Santacroce L, Saini R, Ballini A, Inchingolo F. Oral probiotics influence oral and respiratory tract infections in pediatric population: a randomized double-blinded placebo-controlled pilot study. Eur Rev Med Pharmacol Sci 2018; 22: 8034-8041.